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(54) Title: A PROCESS FOR THE PREPARATION OF BENZIMIDAZOLE DERIVATIVES

(57) Abstract

A new process for the preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and the single enantiomers thereof which compounds by administration inhibit exogenously or endogenously stimulated gastric acid secretion.

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A PROCESS FOR THE PREPARATION OF BENZIMIDAZOLE DERIVATIVES

DESCRIPTION

Field of the invention

The object of the present invention is to provide a process for the preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and its single enantiomers which compounds by administration inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer.

It is a specific primary object of the invention to provide a process which makes it possible to isolate the pure 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate or its single enantiomers, hereinafter called the 5-isomer which includes its single enantiomers, i.e. the (+)-5-isomer and (-)-5-isomer respectively. The compounds are separated from an isomeric mixture of the 5-isomer and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate or its single enantiomers, the latter hereinafter called the 6-isomer which includes its single enantiomers.

Prior art and background of the invention

Benzimidazole compounds have in its 5-membered ring two nitrogen atoms of which only one can have a substituent. The nitrogens in the 5-membered ring are not equivalent if the 6-membered ring is assymmetrically substituted. Thus, different isomers will arise depending on which of the two inequivalent nitrogens is bearing the substituent. These isomers have different properties. For example the 5-isomer shows a higher chemical stability in the solid state making the compound useful in the preparation of pharmaceutical formulations. Therefore it is desirable to isolate the pure 5-isomer from an isomeric mixture of the 5- and 6-isomers. These compounds also show high bioavailability and exhibits a high chemical stability in solution also at acidic pH which make the compound useful for non-enteric coated formulations.

The isomeric mixture of the 5- and 6-isomer is disclosed in PCT/SE91/00415. It is believed that the 5-isomer and the 6-isomer are metabolized into the corresponding compounds carrying H in the N-1 position before exerting their effect. These corresponding compounds are disclosed in PCT/SE91/00416.

Processes to prepare the desired 5-isomer have been tried where the starting compound being a 5-isomer which has a substituent on one of the nitrogen atoms and which can be transformed into the desired nitrogen substituent. However it is difficult to prepare the pure isomers by applying the above mentioned strategy.

Another process tried is to synthesize the sulphide having the desired substituent on one of the nitrogen atoms and by oxidation transfer the sulphide into the desired sulphoxide. The starting compound in these processes could be either in the form of its 5-isomer or the isomeric mixture. When mixtures of structural isomers are

obtained in any of the above processes, the 5-isomer is isolated by means of crystallisation or chromatography.

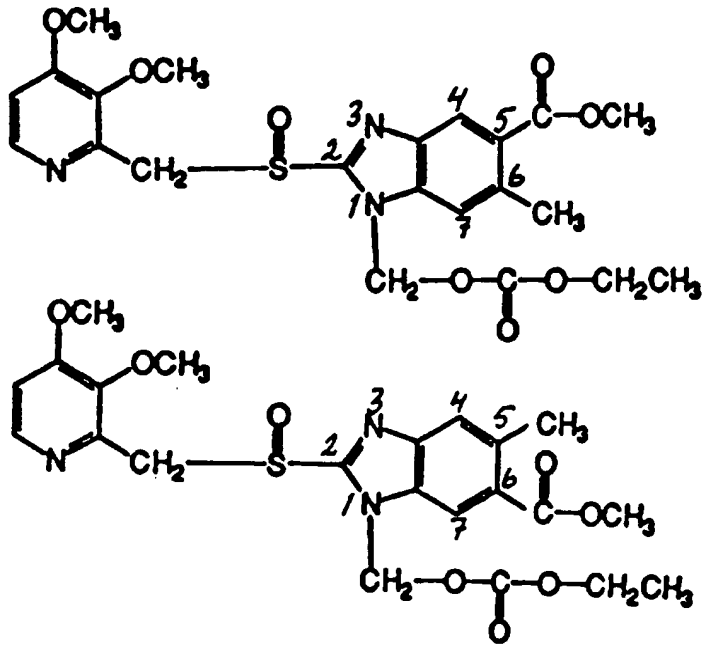
Furthermore, attempts to directly synthesize the pure 5-isomer have not succeeded and attempts to isolate the 5-isomer from an isomeric mixture by recrystallisation or chromatography in various solvents have resulted in poor yields.

A preparative method for use of attack at the 2-position of benzimidazole has been described previously (D.R. Graber, R.A. Morge, J.C. Sih, J. Org. Chem. 1987, 52, 4620-4622). The present application describes a novel and efficient way to obtain the pure 5-isomer.

Outline of the invention

It has now surprisingly been found that by using the difference in chemical reactivity of the 5-isomer (including the single enantiomers thereof) and the 6-isomer (including the single enantiomers thereof) it is possible to isolate the 5-isomer easily. N-substituted benzimidazoles are susceptible to nucleophilic attack on the carbon in the 2-position, and here the 5- and 6-positions can show a high difference in chemical reactivity. This rate difference for a pair of isomers is influenced by solvent characteristics, characteristics of the nucleophile, and the substituent pattern and position of the substituents of the respective isomers. High isomer selectivity in the nucleophilic attack in the 2-position is favoured by electron with-drawing groups in the benzimidazole and by using dipolar aprotic solvents.

Thus, the present invention provides a process for the preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and the single enantiomers thereof by reacting an isomeric mixture of two compounds of the formula I or of the formula Ia or Ib



(I, Ia, Ib)

Ia (+)-enantiomers

Ib (-)-enantiomers

with a suitable nucleophile in a solvent. Preferred nucleophiles are compounds having the formula II

RSH II

wherein R is a straight or branched, substituted or unsubstituted alkyl C_1-C_{12}, preferably a lower alkyl C_1-C_5 unsubstituted or substituted with a hydroxy, carboxy, amino and/or amido group, or R is a substituted or unsubstituted aryl group, preferably a phenyl.

The reaction is yielding the 5-isomer and degradation products from the 6-isomer and from some 5-isomer.

The 6-isomer has a higher rate of chemical reactivity than the 5-isomer and it is thus possible to selectively degrade the 6-isomer in the mixture. Subsequently, the 5-isomer is isolated from the reaction mixture by conventional work-up procedures.

Preferably the reaction is performed in the presence of a base, such as a bicarbonate.

Preferably the solvent is a dipolar aprotic solvent, such as dimethylsulphoxide (DMSO).

Preferably the nucleophile is thiophenol sodium salt, propanethiol sodium salt, ethanethiol sodium salt, n-butylmercaptane, t-butylmercaptane,

2-mercaptoethanol, 1-pentanemercaptane, p-thiocresol, (3,4-dimethoxy-2-pyridinyl)methylthiol or N-acetylcysteine. The most preferred nucleophiles are t-butylmercaptane and 2-mercaptoethanol.

The nucleophile can be added to the reaction either as a salt or as a neutral compound.

The reaction may be performed at temperatures ranging from 0° to 40° C and has been found to be fast at room temperature.

The invention is illustrated by the following examples.

Example 1. Preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate using t-butylmercaptane as nucleophilic agent

Grinded potassium hydrogen carbonate (1.5 g, 15.0 mmol) and a 73:27-mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (3.0 g, 6.0 mmol) were dissolved and suspended, respectively, in DMSO (20 mL) under argon and stirring at room temperature. t-Butylmercaptane (0.3 mL, 2.67 mmol) was added drop-wise with a syringe. The reaction mixture was stirred under argon for 3 hours and then diluted with dichloromethane (50 mL; exothermic) and extracted with water (3*25 mL) to remove DMSO, hydrophilic products and inorganic materials. The combined water phases were extracted with dichloromethane (25 mL). The combined organic phases were dried with anhydrous sodium sulphate, filtered, and evaporated in vacuo to give a yellow

syrup. Crystallisation from hot isopropanol (20 mL) gave almost colourless, needle-shaped, micro-crystals which were washed with a little isopropanol (2*2 mL). Yield: 1,64 g (purity 96%; isomer ratio 98:2).

Example 2. Preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate using 2-mercaptoethanol as nucleophilic agent

Grinded potassium hydrogen carbonate (1.5 g, 15.0 mmol) and a 73:27-mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (3.0 g, 6.0 mmol) were dissolved and suspended, respectively, in DMSO (20 mL) under argon and stirring at room temperature.
2-Mercaptoethanol (0.2 mL, 2.85 mmol) was added drop-wise with a syringe. The reaction mixture was stirred under argon for 10.5 hours and then diluted with dichloromethane (50 mL) and extracted with water (3*25 mL) to remove DMSO, hydrophilic products and inorganic materials. The combined water phases were extracted with dichloromethane (25 mL). The combined organic phases were dried with anhydrous sodium sulphate, filtered, and evaporated in vacuo to give a yellow syrup. Crystallisation from hot ethanol (99.5%; 20 mL) gave almost colourless, needle-shaped, micro-crystals which were washed with a little ethanol (99.5%; 3*2 mL). Yield: 1,29 g (purity 96%; isomer ratio 98:2).

Example 3. Enrichment of 5-isomer in pilot scale

DMSO (140 L) and a 70:30-mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (54 kg, 29.3 mol) were added to a 1000-litre reactor at 18 °C to afford an almost clear solution to which potassium hydrogen carbonate (2.0 kg, 20 mol) was added. t-Butylmercaptane (1.69 L, 14.9 mol) was then added under vigorous stirring. A sample was taken after 50 minutes analysed for isomer composition which was found to be 90:10. Additional t-butylmercaptane (0.3 L, 3.55 mol) was added, the reaction mixture was stirred for additional 45 minutes before a new sample was taken and analysed for isomer composition which was found to be 96:4. The achieved isomer ratio was regarded as satisfactory. Dichloromethane (200 kg/20 min; exothermic reaction) and water (112 kg/5 min) was added and the resulting mixture was first stirred for 20 minutes and then left without stirring for 30 minutes. The water phase was removed and additional water (75 kg) was added and the resulting mixture was first stirred for 15 minutes and then left without stirring for 25 minutes. The water phase was removed and the organic phase was evaporated in vacuo (jacket temperature 30 °C) to give a butter-like residue. Ethanol (104 kg) was added to facilitate removal of residual dichloromethane by evaporation in vacuo (jacket temperature was raised to 50 °C) which continued until a clear solution had been achieved. The clear solution was stirred at approximately 55 °C for approximately 45 minutes and then cooled (cooling rate 50 °C/h). When the temperature of the solution reached 40 °C, water (65 kg) was added under vigorous stirring. When the temperature reached 35 °C, 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (4.5 g) was added to induce

crystallisation. Crystallisation started 15 minutes later at which time stirring was reduced from vigorous to gentle. The resulting slurry of crystals was filtered after 11 hours of gentle stirring at 20 °C. The filter-cake was washed with a water:ethanol mixture (1:3; 2*20 L) and dried to give 16.3 kg off-white crystals (water content 33%; ethanol content 11%; purity by HPLC 97.7%; isomer ratio 97:3).

Example 4. One-pot reaction: synthesis of isomer mixture and enrichment of 5-isomer

Potassium carbonate (156 mg, 1.1 mmol) and 18-crown-6 (60 mg, 0.23 mmol) was added to DMSO (7 mL) under stirring. Then, 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole (400 mg, 0.8 mmol; water content 3.7%; purity 96.7%). When a solution had been achieved after approximately 50 minutes, chloromethyl ethyl carbonate (171 mg, 1.23 mmol) was added. Stirring was continued for 18 hours to afford a clear, dark-yellow, liquid phase and some white particles. Analysis of a sample by HPLC indicated a 94% yield of a 61:39-mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate. Then, t-butylmercaptane (50 μL, 0.46 mmol) was added and allowed to react for 40 minutes before a sample was withdrawn and analysed by HPLC, which indicated that a 74:26 isomer ratio had been achieved. Additional t-butylmercaptane (50 μL, 0.46 mmol) was added and allowed to react for 30 minutes before another sample was withdrawn and analysed by HPLC, which indicated that the isomer ratio had changed to 99:1. The reaction mixture was then diluted with dichloromethane

(3 mL) and extracted with water (3*2 mL) to remove DMSO, hydrophilic products and inorganic materials. The organic phase was evaporated in vacuo to give a syrup. Crystallisation from hot ethanol (99.5%; 5 mL) gave yellowish micro-crystals. Yield: 117 mg (purity 84%; isomer ratio 99:1).

Example 5. Preparation of (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

A mixture of two regio isomers (0.85 g, 1.73 mmol), namely a mixture of (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (≈60%) and(-)-6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate was mixed with potassium hydrogen carbonate (83 mg, 0.83 mmol) and acetonitrile. A dropwise addition of 2-mercaptoethanol (0.12 ml, 1.7 mmol) was followed by stirring at room temperature for one hour. The mixture was evaporated and the residue partitioned between methylene chloride and water. The organic layer was dried over Na_2SO_4 and then evaporated. The oily residue was purified by flash chromatography on silica gel with a mixture of methanol (2-4%) and ammonia saturated methylene chloride as eluent. The product was triturated with ethanol, to give the title compound (0.15 g, 44%) in the form of a white solid, mp. 144-147°C, $[\alpha]_D$=-120.8° (c=1.0%, chloroform).

Example 6. Preparation of (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

A mixture of two regio isomers (0.62 g, 1.26 mmol), namely a mixture of (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-sulfinyl]-1H-

benzimidazole-1-ylmethyl ethyl carbonate (≈65%) and (+)-6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate was mixed with potassium hydrogen carbonate (45 mg, 0.45 mmol) and acetonitrile. A dropwise addition of 2-mercaptoethanol (0.07 ml, 1.0 mmol) was followed by stirring at room temperature for one hour. The mixture was evaporated and the residue partitioned between methylene chloride and water. The organic layer was dried over Na_2SO_4 and then evaporated. The oily residue was purified by flash chromatography on silica gel with acetonitrile as eluent. The product was triturated with ethanol, to give the title compound (0.23 g, 44%) in the form of a white solid, mp. 145-147°C, $[\alpha]_D = +122.7°$ (c=1.0%, chloroform).

Preparation of intermediates

Example 7. Preparation of (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole (1.8 g, 3.3 mmol) was divided into three parts. Each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereoisomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (70/30), but each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their solutions during the hydrolyses; To the acetonitrile/aqueous solutions of the more lipophilic

diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralised with 3.0 M aqueous solutions of NH_4Cl. The solutions from each preparation were combined and extracted with methylene chloride whereupon the organic phases were dried over Na_2SO_4. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylene chloride gradient 1-8%) yielded 250 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 171-173° C. $[a]^{20}_D = +153.1°$ (c=0.5%, chloroform).

Example 8. Preparation of (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole

To the acetonitrile/aqueous solutions of the less lipophilic diastereomer of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole (obtained from the very same reversed phase chromatographic preparations described in Example 7) were added 1.0 M NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralised with 3.0 M aqueous solutions of NH_4Cl. The solutions from each preparation were combined and extracted with methylene chloride whereupon the organic phases were dried over Na_2SO_4. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylene chloride gradient 1-8%) yielded 270 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 173-174° C. $[a]^{20}_D = -150.0°$ (c=0.5%, chloroform).

Example 9. Preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-(R)-mandeloyloxymethyl)-1-H-benzimidazole and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole

A solution of 0.33 g (8.2 mmol) sodium hydroxide in 1.6 ml water was added to a mixture of 1.4 g (4.1 mmol) tetrabutylammonium hydrogen sulphate and 0.62 g (4.1 mmol) of (R)-(-)-mandelic acid. Chloroform (50 ml) and a mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1-(chloromethyl)-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1-(chloromethyl)-1H-benzimidazole (as racemates) were added and the mixture was refluxed for 3 hours. The reaction mixture was chilled and then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and dried over Na_2SO_4. Removal of solvents yielded a diastereomeric mixture of the two regioisomeric mandelic esters. The crude product was used directly in the chromatographic step where the diastereomers were separated (Examples 7 and 8). Yield: 2.4 g, 62%.

Example 10. Synthesis of a mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

To a suspension of 0.45 g (1.1 mmol) of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole and 0.25 g (1.8 mmol) of potassium carbonate anhydrous in 45 ml of dry acetonitrile, 0.21 g (1.5 mmol) of chloromethyl ethyl carbonate dissolved in 5 ml of acetonitrile was added. The reaction mixture was stirred at room temperature over night. The solvent was then removed in vacuo and the residue was diluted with methylene chloride and water. The organic solvent was dried over anhydrous sodium sulphate. Removal of the solvent in vacuo gave the crude product, which was chromatographed with silica gel and eluted with ethyl acetate to provide 0.94 g yellow oil which slowly crystallised. Recrystallisation with ethanol yielded 0.25 g (44 %) of the isomeric mixture of the title.

Example 11. Preparation of (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl))-1H-benzimidazole-1-ylmethyl ethyl carbonate

(-)-5-Carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole (1.0 g, 2.6 mmol) was mixed with potassium carbonate (0.39 g, 2.8 mmol) and acetonitrile (40 ml). Chloromethyl ethyl carbonate (0.36 g, 2.6 mmol) was added and the mixture was stirred over night. After evaporation the residue was partitioned between water (50 ml) and methylene chloride (50 ml). The

aqueous phase was extracted with methylene chloride (50 ml) and the combined organics were dried (Na_2SO_4) and evaporated. The oily residue was triturated with ethanol, to give the title compounds as a regio isomeric mixture (0.95 g, 75%) in the form of a white solid, $[\alpha]_D$= -121.5° (c=0.5%, chloroform).

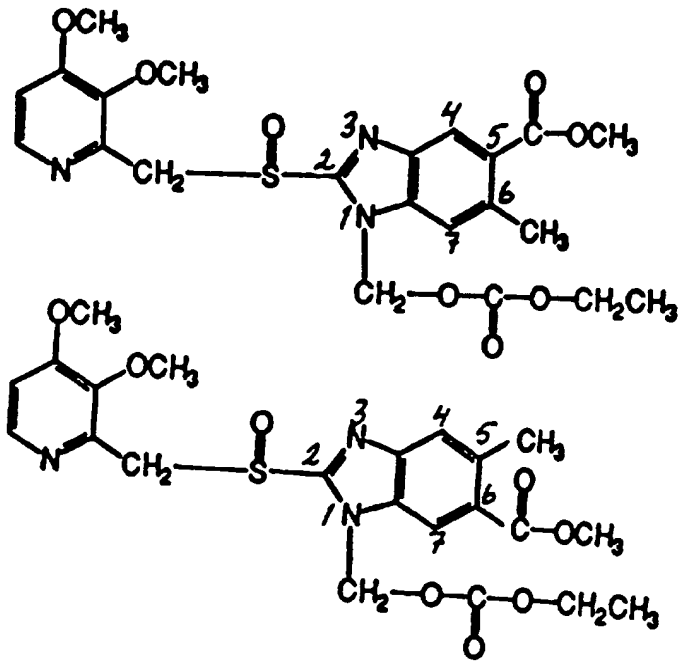
Example 12. Preparation of (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxpyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

(+)-5-Carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole (0.67 g, 1.72 mmol) was mixed with potassium carbonate (0.26 g, 1.89 mmol) and acetonitrile (25 ml). Chloromethyl ethyl carbonate (0.26 g, 1.89 mmol) was added and the mixture was stirred over night. After evaporation the residue was partitioned between water (25 ml) and methylene chloride (50 ml). The aqueous phase was extracted with methylene chloride (50 ml) and the combined organics were dried (Na_2SO_4) and evaporated. The oily residue was purified by flash chromatography on silica gel, with acetonitrile/methylene chloride as eluent, to give the title compounds as a regio isomeric mixture (0.62 g, 73%) in the form of a syrup, $[\alpha]_D$= +108° (c=0.5%, chloroform).

The best way of carrying out the invention at present is according to Example 3.

CLAIMS:

1. A process for the preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and the single enantiomers thereof c h a r a c t e r i z e d in that an isomeric mixture of two compounds of the formula I or of the formula Ia or Ib



(I, Ia, Ib)

Ia (+)-enantiomers

Ib (-)-enantiomers

is reacted with a nucleophile in a solvent whereby the 5-isomer is isolated from the reaction mixture.

2. A process according to claim 1, c h a r a c t e r i z e d in that the nucleophile having the formula II

RSH II

wherein R is a straight or branched, substituted or unsubstituted alkyl C_1-C_{12} or a substituted or unsubstituted aryl.

3. A process according to claim 2, c h a r a c t e r i z e d in that R is a straight or branched lower alkyl C_1-C_5 unsubstitued or substituted with a hydroxy, carboxy, amino and/or amido group; or a phenyl group.

4. A process according to claim 2, c h a r a c t e r i z e d in that the nucleophile is thiophenol sodium salt, propanethiol sodium salt, ethanethiol sodium salt, n-butylmercaptane, t-butylmercaptane, 2-mercaptoethanol, 1-pentanemercaptane, p-thiocresol, N-acetylcysteine or (3,4-dimethoxy-2-pyridinyl)methylthiol.

5. A process according to claim 4, c h a r a c t e r i z e d in that the nucleophile is t-butylmercaptane or 2-mercaptoethanol.

6. A process according to claim 1, c h a r a c t e r i z e d in that the solvent is a dipolar aprotic solvent.

7. A process according to claim 6, c h a r a c t e r i z e d in that the solvent is dimethyl sulphoxide.

8. A process according to claim 1, c h a r a c t e r i z e d in that the reaction is performed in the presence of a base.

9. A process according to claim 8, c h a r a c t e r i z e d in that the base is a bicarbonate.

10. 5-Carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate prepared by a process according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01414

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ACTA CHEMICA SCANDINAVICA, Volume 43, 1989, Arne Brändström et al, "Chemical Reactions of Omeprazole and Omeprazole Analogues. II. Kinetics of the Reaction of Omeprazole in the Presence of 2-Mercaptoethanol" page 549 - page 568 --	1-10
A	J. ORG. CHEM., Volume 52, 1987, David R. Graberet et al, "Reaction of 2-(Alkylsulfinyl)-, 2(Arylsulfinyl)-, and 2-(Aralkylsulfinyl) benzimidazoles with Thios: A Convenient Synthesis of Unsymmetrical Disulfields" page 4620 - page 4622 --	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 1996	02 -04- 1996
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